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1635

THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Jiandong Chen, Sudhir Agrawal and Ruiwen Zhang		
Application No.:	09/541,848	Group:	1635
Filed:	April 3, 2000	Examiner:	James Schultz
Confirmation No.:	4238		
For:	MDM2-SPECIFIC ANTISENSE OLIGONUCLEOTIDES		

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APPEAL BRIEF

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Sir:

Applicants hereby appeal the Examiner's final rejection of the claims of the above-identified patent application.

Real party in interest

The real party in interest is Hybridon, Inc.

Related appeals and interferences

There are no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Status of the claims

Claims 1-13, 17-20, 22, 24, 26, and 28 are pending and are hereby appealed. Claim 16 is pending and allowable. Claims 14-16, 21, 23, 25, 27 and 29 are canceled.

Statement of amendments

No amendments have been made subsequent to final rejection.

Summary of the invention

The invention provides a method for using improved antisense oligonucleotides complementary to a portion of the MDM-2-encoding RNA to inhibit expression of the MDM-2 gene. (page 16, lines 17-18; page 17, lines 7-8). The invention further provides a method for using improved antisense oligonucleotides complementary to a portion of the MDM-2-encoding RNA to inhibit tumor growth *in vivo*. (page 26, lines 5-11; page 29, lines 12-14). The invention also provides methods for using improved antisense oligonucleotides complementary to a portion of the MDM-2-encoding RNA in conjunction with chemotherapeutic agents (page 29, lines 14-16) or radiation (original claim 4). The invention further provides a method for using improved antisense oligonucleotides complementary to a portion of the MDM-2-encoding RNA to increase p53 concentration (page 28, lines 5-7).

Issues

The issue is whether claims 1-13, 17-20, 22, 24, 26, and 28 are enabled by the specification.

Grouping of the claims

The claims appealed stand or fall together.

Argument

Applicants respectfully submit that the presently maintained rejection is in error because the Examiner failed to consider the relevant precedents cited by the Applicants or to apply relevant Patent and Trademark policy. Applicants respectfully submit that one skilled in the art would be taught by the specification how to practice the claimed invention without undue experimentation. The specification accurately teaches how to practice the claimed invention. One skilled in the art could easily reproduce Applicants' results by simply following the examples and the disclosed oligonucleotides. As to other oligonucleotides, undoubtedly some screening using the methods disclosed in the specification and examples would be required. However, these experiments, which would require no modification of the disclosed assays, would not be undue. Such experimentation would be required no matter how many oligonucleotides were exemplified in the specification.

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. See M.P.E.P. §2164.01 In the antisense field, scientists typically engage in such screening, and would have to do so no matter how many oligonucleotides are exemplified. In addition, the enablement requirement is met if the description enables any mode of making and using the invention. *Johns Hopkins University v. Cell Pro Inc.*, 152 F.3d 1342, 1360; 47 U.S.P.Q.2d 1705, 1718 (Fed. Cir. 1998), *citing Engel Indus., Inc. v. Lockformer Co.*, 20 U.S.P.Q.2d 1300, 1304 (Fed. Cir. 1991). Applicants have clearly met this requirement.

In *Johns Hopkins University v. Cell Pro Inc.*, the patentee claimed a genus of antibodies which bound to a particular antigen. Cell Pro argued that the specification enabled only a single antibody and that it would require undue experimentation to produce other antibodies within the genus. The Federal Circuit disagreed. It stated that the test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *Id.*

The present case is exactly analogous. The specification teaches exactly how to proceed to enable the desired generic embodiment of the claims. Only routine experimentation,

following the guidance of the specification, would be required to practice the claimed methods using antisense oligonucleotides and chemotherapeutic agents other than those exemplified in the specification.

Accordingly, the rejection of Claims 1-13, 17-20, 22, 24, 26 and 28 for non-enablement was in error. Applicants therefore request the Board to overturn the rejection and instruct the Examiner to withdraw the rejection and allow the claims.

Respectfully submitted,

Date: 10/25/04

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Appendix

Claims involved in the appeal

1. A method of inhibiting expression of MDM2 in a mammal, the method comprising administering to the mammal an effective MDM2-expression inhibiting amount of an anti-MDM2 antisense oligonucleotide, wherein said antisense oligonucleotide comprises from about 8 to about 50 nucleotides that inhibits MDM2 protein expression, said oligonucleotide binding to mdm2-encoding RNA and being complementary to a sequence that overlaps by at least one nucleotide a sequence within the mdm2 RNA, which sequence within the mdm2 RNA is selected from the group consisting of SEQ ID NOS: 2, 3, 4, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24.

2. The method according to claim 1 comprising co-administering a cancer chemotherapeutic agent.

3. The method according to claim 2, wherein the cancer therapeutic agent is 10-hydorxycamptothecin, adriamycin, or 5-fluorouracil.

4. The method according to claim 1 comprising co-treating the mammal with anti-cancer levels of radiation.

5. A method of inhibiting cancer *in vivo*, the method comprising administering a cancer-inhibiting amount of an anti-MDM2 antisense oligonucleotide, wherein the cancer involves over expression of MDM2, wherein said antisense oligonucleotide

comprises from about 8 to about 50 nucleotides that inhibits MDM2 protein expression, said oligonucleotide binding to mdm2-encoding RNA and being complementary to a sequence that overlaps by at least one nucleotide a sequence within the mdm2 RNA, which sequence within the mdm2 RNA is selected from the group consisting of SEQ ID NOS: 2, 3, 4, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24.

6. The method according to claim 5, wherein the cancer is selected from the group consisting of osteosarcoma, soft tissue sarcoma, breast cancer, ovarian cancer, cervical cancer, oral squamous cell carcinoma, brain tumor, esophageal cancer, colorectal carcinoma, bladder cancer, urithelial carcinoma, leukemia, and large B cell lymphoma.

7. The method according to claim 5 comprising co-administering an effective cancer-treating amount of a cancer chemotherapeutic agent.

8. The method according to claim 7, wherein the cancer chemotherapeutic agent is 10-hydorxycamptothecin, adriamycin, or 5-fluorouracil.

9. The method according to claim 5 comprising co-treating the mammal with anti-cancer levels of radiation.

10. A method of increasing p53 concentration, the method comprising administering to the cell or to an animal comprising the cell an effective MDM2-expression inhibiting

amount of an anti-MDM2 antisense oligonucleotide, wherein said antisense oligonucleotide comprises from about 8 to about 50 nucleotides that inhibits MDM2 protein expression, said oligonucleotide binding to mdm2-encoding RNA and being complementary to a sequence that overlaps by at least one nucleotide a sequence within the mdm2 RNA, which sequence within the mdm2 RNA is selected from the group consisting of SEQ ID NOS: 2, 3, 4, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24.

11. The method according to claim 10 comprising co-administering a cancer chemotherapeutic agent.

12. The method according to claim 11, wherein the cancer chemotherapeutic agent is 10-hydorxycamptothecin, adriamycin, or 5-fluorouracil.

13. The method according to claim 10 comprising co-treating the mammal with anti-cancer levels of radiation.

17. The method according to claims 1, 5 or 10, wherein the antisense oligonucleotide has a nucleotide base sequence set forth in Sequence Listing as SEQ ID NO:36.

18. The method according to claims 1, 5 or 10, wherein the antisense oligonucleotide has a nucleotide base sequence set forth in Sequence Listing as SEQ ID NO:27, 28, 29, 30, 31, 32, 33, and 34.

19. The method according to claims 1, 5 or 10, wherein the antisense oligonucleotide has a nucleotide base sequence set forth in Sequence Listing as SEQ ID NO:35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, and 46.

20. The method according to claims 1, 5 or 10, wherein the oligonucleotide has at least one internucleotide linkage selected from the group consisting of phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phophoramidate, bridged methylene phosphonate, bridged phosphorothioate, and sulfone internucleotide linkages.

22. The method according to claim 20, wherein the antisense oligonucleotide comprises an RNase H activating segment of four or more consecutive phosphodiester and/or phosphorothioate internucleotide linkages.

24. The method according to claim 22, wherein RNase H activating segment is flanked on both sides by a segment of two or more nucleotides that are modified to increase nuclease resistance and/or target hybridization affinity.

26. The method according to claim 24, wherein the nucleotides of the segments of 2 or more nucleotides are 2'-substituted ribonucleotides.

28. The method according to claim 26, wherein the 2'-substituted nucleotides are substituted at their 2' position with methoxy or methoxyethoxy.

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ENCLOSURES *(Check all that apply)*

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